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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,117	02/27/2002	David W. Morris	PP23697.0001/20366-005001	7176

55255 7590 02/26/2009

Novartis Vaccines and Diagnostics, Inc.
Corporate Intellectual Property
P.O. BOX 8097
EMERYVILLE, CA 94662-8097

EXAMINER	
AEDER, SEAN E	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
02/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/8/09 has been entered.

Claims 24, 26, 27, 29, and 37-39 are pending.

Claims 24, 26, 27, 29, 38, and 39 have been amended by Applicant.

Claims 24, 26, 27, 29, and 37-39 are currently under consideration.

This Office Action contains New Rejections necessitated by amendments.

Objections Withdrawn

The Objection to claim 38 is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention, for the reasons stated in the Office Action of 7/8/08 and for the reasons set-forth below.

Claim 38 is rejected as indefinite for reciting "highly" stringent hybridization conditions, as the specification does not distinctly define the limitations of such conditions. For example, the specification teaches exemplary stringent conditions include hybridization at 60C in a solution with a sodium ion concentration from about 0.01 to 1.0M, pH 7.0 to 8.3 comprising formamide (page 11, in particular). However, those conditions are not *defined* by the claims and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This rejection can be obviated by distinctly defining the conditions, ***including washing conditions***, under which highly stringent conditions are practiced.

In the Reply of 1/8/09, Applicant argues that claim 38 recites that hybridization is performed at 60C in a solution with a sodium ion concentration from about 0.01 to 1.0M, pH 7.0 to 8.3 comprising formamide and concludes that claim 38 recites high stringent hybridization conditions. Applicant further argues that one of skill could readily determine suitable washing conditions because high stringency conditions are known in the art.

The amendments to the claims and the arguments found in the Reply of 1/8/09 have been carefully considered, but are not deemed persuasive. It is noted that claim 38 recites that hybridization is performed at 60C in a solution with a sodium ion concentration from about 0.01 to 1.0M. However, it is the Office's position that the

metes and bounds of “highly” stringent hybridization conditions are not clear without defining washing conditions of “highly” stringent hybridization conditions.

In regards to the argument that one of skill could readily determine suitable washing conditions because high stringency conditions are known in the art, the Examiner agrees that one could identify many different washing conditions. However, it is unclear which washing conditions are encompassed by the recited methods involving “highly” stringent hybridization conditions.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 26, 27, 29, and 37-39 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons stated in the Office Action of 7/8/08 and for the reasons set-forth below.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to methods wherein a decrease of at least 50% in a level of expression of nucleic acids comprising SEQ ID NO:167, full complements of SEQ ID NO:167, and just any nucleic acid that hybridizes under highly stringent conditions to SEQ ID NO:167 or the complete complement thereof in a patient sample as compared to a second sample indicates the patient has colon cancer.

The specification discloses that SEQ ID NO:167 is a cancer associated (CA) nucleic acid (page 10 lines 9-12 and table 1, in particular). The specification further discloses that CA nucleic acids are nucleic acids that were identified through use of oncogenic retroviruses, whose sequences insert into the genome of lymphatic tissue resulting in carcinoma (page 3 lines 17-29 and page 7 lines 20-24, in particular). The specification further discloses that CA nucleic acids can be downregulated in carcinomas *and* discloses that CA nucleic acids can be upregulated in carcinomas (see lines 29-38 on page 7, in particular). *However*, of the hundreds of CA nucleic acids disclosed in the specification (see Table 1), the specification does not disclose which CA nucleic acids are upregulated and which are downregulated in particular carcinomas. Further, the specification lacks working examples demonstrating methods

wherein a decrease of at least 50% in a level of expression of a nucleic acid (including nucleic acids comprising SEQ ID NO:167, full complements of SEQ ID NO:167, and just any nucleic acid the hybridizes under highly stringent conditions to SEQ ID NO:167 or the complete complement thereof) in a patient sample as compared to a second sample indicates the patient has colon cancer.

The level of unpredictability for using a particular expression pattern of a particular molecule to detect any disease is quite high. The state of the prior art dictates that one of skill in the art would not predict that a particular expression pattern of a particular molecule is indicative of a particular diseased state without a demonstration that said particular diseased stated correlates with said particular expression pattern of said particular molecule. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained

from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence demonstrating a particular expression pattern of a particular molecule correlating with a particular diseased state, one of skill in the art would not predict said particular expression pattern of said particular molecule correlates with said particular diseased state without undue experimentation. Experimentation to identify such a correlation would in itself be inventive.

Since neither the specification nor the prior art provide evidence of methods wherein a decrease of at least 50% in a level of expression of nucleic acids comprising SEQ ID NO:167, full complements of SEQ ID NO:167, and just any nucleic acid that hybridizes under highly stringent conditions to SEQ ID NO:167 or the complete complement thereof in a patient sample as compared to a second sample indicates the patient has colon cancer, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

In the Reply of 1/8/09, Applicant has amended the claims and argues that the claims no longer recite contradictory methods. Applicant further states that the claimed methods do not relate to hundreds of CA nucleic acids. Applicant further states that the claims relate to nucleic acids having a particular sequence, SEQ ID NO:167 or the full complement thereof, and nucleic acids at least 98% identical to nucleic acids set-forth in SEQ ID NO:167. Applicant further argues that Tockman et al is not relevant when considering whether an invention is enabled under 35 U.S.C. 112, first paragraph, because Tockman et al discusses steps of brining a biomarker into clinical application and MPEP 2164 states that it is not necessary to enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment. Applicant further argues that Tockman et al does not suggest that a biomarker that has not been validated for use in the clinic is not suitable as a biomarker "in general". Applicant further argues the specification enables one of ordinary skill in the art to practice the claimed methods without undue experimentation because one of skill in the art can readily determine if expression of a nucleic acid having the nucleotide sequence set-forth in SEQ ID NO:167, or a nucleic acid having at least 98% identity to SEQ ID NO:167 is decreased relative to a control sample. Applicant points to claim 38 and further states that one of ordinary skill in the art can readily determine if the amount of

duplex formed upon contacting a polynucleotide that hybridizes under highly stringent conditions to a nucleic acid having the nucleic acid sequence set forth in SEQ ID NO:167 or the full complement thereof with a patient sample is decreased relative to the amount of duplex formed by hybridization of such a polynucleotide to a non-cancer sample.

The amendments to the claims and the arguments found in the Reply of 1/8/09 have been carefully considered, but are not deemed persuasive. It is agreed that the amended claims no longer recite contradictory methods.

In regard to the arguments that the claimed methods do not relate to hundreds of CA nucleic acids and that the claims relate to nucleic acids having a particular sequence, SEQ ID NO:167 or the full complement thereof, and nucleic acids at least 98% identical to nucleic acids set-forth in SEQ ID NO:167, the claims relate to a very large number of nucleic acids. The claims relate to methods of detecting any nucleic acid 98% identical to SEQ ID NO:167, methods of detecting any nucleic acid fully complementary to any nucleic acid 98% identical to SEQ ID NO:167, and methods of detecting any nucleic acid that hybridizes under highly stringent conditions to SEQ ID NO:167 or the complement thereof.

In regards to the argument that Tockman et al is not relevant when considering whether an invention is enabled under 35 U.S.C. 112, first paragraph, Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to

support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). Tockman is cited to address these factors, mainly the predictability factor and the state of the prior art factor. Tockman et al teaches the state of the art is such that the level of unpredictability for using a particular expression pattern of a particular molecule to detect any disease is quite high without a demonstration of said particular expression pattern correlating with said particular disease.

In regards to the argument that Tockman et al does not suggest that a biomarker that has not been validated for use in the clinic is not suitable as a biomarker "in general", Applicant is arguing limitations not recited in the claims. The claims are not drawn to using a biomarker as a "general" biomarker. Rather, the claims are drawn to methods of using a biomarker to detect a distinct disease. The amount of guidance or direction needed to enable an invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Therefore, while little guidance is needed to merely detect a defined polynucleotide, much more guidance is needed to enable a method of diagnosing a particular disease based on a particular expression pattern of

any of the polynucleotides encompassed by the instant claims due to the unpredictability of the art and the lack of knowledge in the art that a particular expression pattern of just any of the polynucleotides encompassed by the instant claims correlates with a particular diagnosis.

In regards to the argument that the specification enables one of ordinary skill in the art to practice the claimed methods without undue experimentation because one of skill in the art can readily determine if expression of a nucleic acid having the nucleotide sequence set-forth in SEQ ID NO:167 or a nucleic acid having at least 98% identity to SEQ ID NO:167 is decreased relative to a control sample, it is acknowledge that one of skill in the art can readily determine differences in expression levels. However, it is not predictable that such differences are indicative of colon cancer for the reasons discussed above.

In regards to the argument that one of ordinary skill in the art can readily determine if the amount of duplex formed upon contacting a polynucleotide that hybridizes under highly stringent conditions to a nucleic acid having the nucleic acid sequence set forth in SEQ ID NO:167 or the full complement thereof with a patient sample is decreased relative to the amount of duplex formed by hybridization of such a polynucleotide to a non-cancer sample, Applicant is arguing limitations not recited in the claims. The claims do not recite methods wherein an amount of duplex formed upon contacting a polynucleotide that hybridizes under highly stringent conditions to a nucleic acid having the nucleic acid sequence set forth in SEQ ID NO:167 or the full complement thereof with a patient sample is decreased relative to the amount of duplex

formed by hybridization of such a polynucleotide to a non-cancer sample. Rather, claim 38 encompasses methods wherein probes are used to detect biomarkers in patient samples wherein said biomarkers are polynucleotide that hybridizes under highly stringent conditions to a nucleic acid having the nucleic acid sequence set forth in SEQ ID NO:167 or the full complement thereof.

New Rejections Necessitated by Amendments

Claims 24, 26, 27, 29, and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claims 24, 26, 27, 29, 37, and 39 recite methods wherein a decrease of at least 50% in the level of expression of nucleic acids comprising a sequence at least 98% identical to SEQ ID NO:167 or the full complement thereof in a patient sample relative to a control sample indicates that patient has colon cancer. Descriptions of methods wherein a decrease of at least 50% in the level of expression of nucleic acids comprising a sequence at least 98% identical to SEQ ID NO:167 or the full complement thereof in a patient sample relative to a control sample indicates that patient has colon cancer are not found in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

Claim 38 recites methods wherein a decrease of at least 50% in the level of expression of nucleic acids comprising a sequence that hybridizes under highly stringent conditions to SEQ ID NO: 167 or the complement thereof in a patient sample relative to a control sample indicates that patient has colon cancer. Descriptions of methods wherein a decrease of at least 50% in the level of expression of nucleic acids comprising a sequence that hybridizes under highly stringent conditions to SEQ ID NO: 167 or the complement thereof in a patient sample relative to a control sample indicates that patient has colon cancer are not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

The specification discloses that SEQ ID NO:167 is a cancer associated (CA) nucleic acid (page 10 lines 9-12 and table 1, in particular). The specification further discloses that CA nucleic acids are nucleic acids that were identified through use of oncogenic retroviruses, whose sequences insert into the genome of lymphatic tissue resulting in carcinoma (page 3 lines 17-29 and page 7 lines 20-24, in particular). The specification further discloses that CA nucleic acids can be downregulated in carcinomas *and* discloses that CA nucleic acids can be upregulated in carcinomas (see lines 29-38 on page 7, in particular). *However*, of the hundreds of CA nucleic acids disclosed in the specification (see Table 1), the specification does not disclose which CA nucleic acids are upregulated and which are downregulated in particular

carcinomas. Further, the specification lacks working examples demonstrating methods wherein a decrease of at least 50% in a level of expression of a nucleic acid (including nucleic acids comprising SEQ ID NO:167, full complements of SEQ ID NO:167, and just any nucleic acid the hybridizes under highly stringent conditions to SEQ ID NO:167 or the complete complement thereof) in a patient sample as compared to a second sample indicates the patient has colon cancer.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642